Published in final edited form as:
J Org Chem. 2002 October 4; 67(20): 6911–6915.

Rapid Syntheses of Benzopyrans from *o*-OBOC Salicylaldehydes and Salicyl alcohols: A Three-Component Reaction

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Abstract

The Diels-Alder reactions of *o*-quinone methides generated from OBOC-salicylic aldehydes and alcohols are described, allowing for the synthesis of various substituted benzopyrans. The low temperatures employed for this procedure enable high diastereoselectivity in reactions with *β*-substituted *o*-quinone methides.

Introduction

The benzopyran “chroman” nucleus is found in a variety of therapeutic agents.[1] Our interest in structurally diverse benzopyrans such as the COX-2 inhibitor diinsininol **1**[2] and the helicase inhibitor heliquinomycin **2**[3] prompted us to consider methods for rapidly fashioning benzopyrans containing ample functionality. We recently described a new facile method for generating *o*-quinone methides in situ from *o*-OBOC salicylic aldehydes and alcohols and examined their reactivity in 1,4-conjugate additions.[4] We now report the extension of this procedure for the construction of a diverse range of benzopyrans.

o-Quinone methides (*o*-QMs) are extremely reactive, undergoing dimerization or trimerization[5] in the absence of a nucleophile or electron-rich alkene. To account for this reactivity, the *o*-QM concentration must be kept low throughout the reaction. Therefore, various methods have been engineered to generate these species in the presence of the nucleophile necessary for the next reaction, allowing for the generation and immediate consumption of the *o*-QM. Naturally, the first applications involved *intramolecular* cyclization motifs.[6] There are only a few accounts of successful *intermolecular* applications.[7] Most are complicated by the preparation of the *o*-QM because they rely on high temperatures or powerful Lewis acids for their generation; therefore, the range of nucleophiles is severely limited as is the ultimate diastereoselectivity in [4+2] cycloadditions.

Building upon an account of McLoughlin,[8] we reported that *o*-OBOC salicylaldehydes and salicyl alcohols could lead to *β*-substituted and *β*-unsubstituted *o*-QMs, respectively, at low temperature upon the addition of an organometallic reagent (Scheme 1).[4a,b] Herein, we report our observations regarding the generation of **3** and **4** and their performance in subsequent inverse electron demand [4+2] cycloaddition reactions with various styrenes, enol ethers, enamines, imines, and heteroaromatics. As can be seen, the mild low-temperature procedure allows three components to be combined in a single pot, thereby producing a vast array of assorted benzopyrans.

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Supporting Information Available: Spectral data for compounds **5**–**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

To generate the *o*-QM from alcohol **3** or aldehyde **4**, an organomagnesium reagent is added. For more precise control, an organolithium reagent is added, followed by the addition of $MgBr_2 \cdot OEt_2$. In both cases, the addition results in a metal alkoxide intermediate that attacks the neighboring BOC residue. A migration ensues resulting in a phenoxide that, if M = Mg, undergoes *β*-elimination of the benzylic OBOC residue to form an *o*-QM. When M = Li, *β*-elimination does not occur until addition of MgX_2 or LiX, which both act as Lewis acid catalysts. When the *o*-QM is generated in the presence of an electron-rich alkene, a diastereoselective [4+2] cycloaddition ensues to afford primarily a cis 1,3-substituted benzopyran.

Results and Conclusions

As shown in Table 1, the process proves quite general and far more convenient than previous methods involving *o*-QMs. Since the cycloaddition occurs between −78 and −10 °C it is much more sensitive to electronic effects and proceeds with better stereoselectivity than previous methods. Moreover, the pliable nature of the procedure allows many substituents to be introduced at the benzylic carbon of the benzopyran nucleus through variations in the organometallic reagent used to initiate formation of the *o*-QM. Although non-*β*-substituted *o*-QMs appear to be more reactive than their *β*-substituted counterparts, *β*-substituted *o*-QMs generated in this manner still undergo reaction with both activated and inactivated alkenes in respectable yields. For example, styrene (**17**) adds to the *o*-QM generated from alcohol **3** by the addition of *t*-BuMgCl (**26**) to produce **5** in 50%. On the other hand, addition of **17** to the *o*-QM generated by the addition of MeMgCl (**31**) to aldehyde **4** proceeds in only 27%. In both of these examples, styrene (**17**) was used as the solvent to maximize the percent yield.

More reactive alkenes proceed with better stereoselectivity and require fewer molar equivalents relative to the *o*-QM. For example, ethyl vinyl ether (10 equiv) adds to the various *β*-substituted *o*-QMs generated from **4** (entries 3–5, Table 1) with a greater than 50:1 preference in the corresponding cis:trans ratio. The *cis*-2-ethoxy-4-phenylbenzopyran (**7**), the *cis*-2-ethoxy-4-vinylbenzopyran (**8**), and the *cis*-2-ethoxy-4-(dimethylphenylsilyl)-benzopyran (**9**) are assembled from three components: an aldehyde, an enol ether, and the necessary organometallic reagents (cf. **28**, **29**, and **30**[9]). Although more congested enol ethers, such as those disubstituted in a vicinal or geminal fashion, prove to undergo less stereo-selective cycloadditions, the results are still quite satisfactory. Addition of Grignard **31** to aldehyde **4** in the presence of dihydropyran (**19**, 10 equiv) proceeds to **10** with a 24:1 ratio of cis:trans isomers. The enol ether **20**,[10] which presents two groups (−OMe and −Ph) capable of secondary orbital interactions, affords **11** with 4:1 selectivity, apparently favoring the endo approach of the phenyl residue.

Other noteworthy adducts include the combination of *o*-QMs with enamines **21**–**23** and imine **24** (entries 8–11, Table 1). The reactions proceed quite rapidly in good overall yield. For example, the *E*-configured vinylogous amide **21**[11] smoothly undergoes cycloaddition with the *o*-QM that is generated by the addition of MeLi (**32**) to aldehyde **4** followed by the addition of $MgBr_2 \cdot OEt_2$. However, the initial cycloadduct proves to be unstable and the pyrrolidine is eliminated upon chromatography to yield the chromene **12**. In a somewhat analogous fashion, the cycloadduct that emerges from addition of enamine **22**[12] to the same *o*-QM undergoes pyrrolidine hydrolysis and hydrate collapse upon chromatography to produce the ketone **13**. On the other hand, cycloaddition of trisubstituted enamine **23** with the *β*-vinyl substituted *o*-QM, generated by addition of vinyl Grignard **29** to aldehyde **4**, proceeds to the apparently more stable cycloadduct **14**. However, stirring **14** with acid does lead to the corresponding chromene by elimination of the morpholine residue. The reaction between imine **24** and the *o*-QM generated by addition of **31** to aldehyde **4** proceeds to **15** in the highest yield of all 2*π* donors examined. Interestingly, the stereochemistry is trans, suggesting an exo-oriented combination

of reactants. Most likely, however, the cis isomer can undergo an intramolecular equilibration to the more thermodynamically stable trans conformation, a process facilitated by the Lewis acid $MgBr_2$ (Figure 2). Generation of an *o*-QM in the presence of a heterocyclic aromatic also yields benzopyrans in high regioselectivity and diastereoselectivity. The addition of methyl Grignard **31** to aldehyde **4** in the presence of furan affords adduct **16** (entry 12, Table 1) in 76% yield. The regiochemistry is explained by analysis of the HOMO of furan, in which the 2-position has the highest orbital coefficient. This predicts the furan oxygen will be at the 3-position in the cycloadduct.

A wide assortment of benzopyrans are produced with excellent diastereoselectivity via inverse electron demand [4+2] cycloadditions with use of this low-temperature method for generating *o*-QMs from *o*-OBOC salicylaldehydes and alcohols. The 2π donors tested include the following in the order of reactivity: imines > enamines > enols > furans > styrenes. Future goals will include the application of this procedure in syntheses of diverse benzopyrans and other natural products, as well as adaptation of the cycloaddition to an asymmetric format. Developments will be reported in due course.

Experimental Section

General Information

These reactions required reagents of the highest quality. All reagents were newly purchased or freshly prepared. Starting aryl aldehydes that were not scrupulously dried often led to lower than expected yields. All column chromatography was conducted with silica gel, eluting with the indicated solvent system. The stereochemistry is established via ^{1}H NMR by analysis of ^{1}H-couplings and NOE interactions.

5: To a flame-dried 5-mL vial was added alcohol **3** (24.0 mg, 0.071 mmol). Styrene (**17**, 0.71 mL) was added, and the vial was cooled to −78 °C. To this mix was added *t*-BuMgCl (**26**, 53 μL, 0.106 mmol, 2 M in Et_2O) dropwise. The reaction was allowed to slowly warm to rt and was monitored by TLC. Upon completion, the reaction was quenched with 0.1 M HCl and extracted with Et_2O. After the ether layer was washed with brine, the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel eluting with 99:1 petroleum ether/ethyl acetate, yielding **5** as a white solid (11.5 mg, 50% yield). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.44–7.31 (m, 5H), 7.07 (d, 1H, J = 8.24 Hz), 6.75 (d, 1H, J = 2.38 Hz), 6.70 (dd, 1H, J_1 = 8.24 Hz, J_2 = 2.38 Hz), 5.06 (dd, 1H, J_1 = 10.15 Hz, J_2 = 2.47 Hz), 3.01–2.93 (m, 1H), 2.82–2.76 (m, 1H), 2.25–2.19 (m, 1H), 2.13–2.03 (m, 1H), 1.56 (s, 9H); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 155.7, 152.2, 150.3, 141.6, 130.0, 128.7, 128.1, 126.2, 119.6, 113.6, 110.2, 94.6, 83.6, 30.0, 27.9, 24.9; IR [CH_2Cl_2, ν_{max} cm^{-1}] 3627, 2936, 1756, 1733; MS (EI) *m*/*z* 226 (78), 104 (24), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}O_4$ 326.1518, found 326.1528.

6: To a flame-dried 5-mL vial was added aldehyde **4** (39.6 mg, 0.12 mmol). Styrene (**17**, 0.59 mL), and Et_2O (0.59 mL) were added, and this mixture was cooled to −20 °C. MeLi (**27**, 88 μL, 0.123 mmol, 1.4 M in Et_2O) was added dropwise, and the resulting solution was stirred for 15 min at −20 °C. After $MgBr_2$·OEt2 (37.0 mg, 0.14 mmol) was added to the solution, the reaction was slowly warmed to room temperature. Upon completion, as noted by TLC, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine, and the combined aqueous layers were saturated with NaCl. The saturated aqueous layer was washed with Et_2O; the combined Et_2O extracts were dried over Na_2-SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel eluting with petroleum ether, yielding **6** as a white solid (10.7 mg, yield 27%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.46–7.34 (m, 5H), 7.28–7.25 (m, 1H), 6.76–6.73 (m, 2H), 5.10–5.07 (m, 1H), 3.20–

3.14 (m, 1H), 2.24–2.19 (m, 1H), 1.81 (q, 1H, J = 11.7 Hz), 1.56 (s, 9H), 1.36 (d, 3H, J = 6.78 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 155.5, 152.2, 150.3, 141.6, 128.8, 128.2, 127.8, 126.3, 125.0, 113.7, 110.1, 94.6, 83.7, 40.0, 30.1, 27.9, 20.3; IR [CH_2Cl_2, ν_{max} cm^{-1}] 3054, 2930, 1757; MS (EI) *m*/*z* 240 (57), 225 (59), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1682.

7: To a flame-dried 5-mL vial was added aldehyde **4** (51.9 mg, 0.15 mmol). Ethyl vinyl ether (**18**, 1 mL) was added and the vial was cooled to −78 °C. To this mixture was added PhMgBr (**28**, 192 μL, 0.18 mmol, 0.96 M in THF) dropwise. The reaction was allowed to slowly warm to rt and was monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The ether layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was then chromatographed through silica gel, eluting with 98:2 petroleum ether/ethyl acetate, yielding **7** as a white solid (41.3 mg, yield 73%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.35–7.30 (m, 2H), 7.28–7.24 (m, 1H), 7.21–7.19 (m, 2H), 6.75 (d, 1H, J = 2.38 Hz), 6.69 (dd, 1H, J_1 = 8.42 Hz, J_2 = 0.92 Hz), 6.60 (dd, 1H, J_1 = 8.42 Hz, J_2 = 2.38 Hz), 5.27 (dd, 1H, J_1 = 8.61 Hz, J_2 = 2.38 Hz), 4.18–4.14 (m, 1H), 4.11–4.03 (m, 1H), 3.71–3.63 (m, 1H), 2.41–2.36 (m, 1H), 2.23–2.15 (m, 1H), 1.56 (s, 9H), 1.27 (t, 3H, J = 7.05 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 154.2, 152.1, 150.6, 144.0, 130.1, 128.8, 127.0, 123.6, 114.0, 110.2, 99.9, 94.6, 83.7, 64.7, 41.2, 37.3, 27.9, 15.4; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2982, 1757; MS (EI) *m*/*z* 311 (34), 224 (56), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{26}O_5$ 370.1780, found 370.1783.

8: To a flame-dried 5-mL vial was added aldehyde **4** (78.8 mg, 0.23 mmol). Ethyl vinyl ether (**18**, 2.3 mL) was added and the vial was cooled to −78 °C. To this mixture was added vinylmagnesium bromide (**29**, 270 μL, 0.25 mmol, 0.955 M in THF) dropwise. The reaction was slowly warmed to room tempearture and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$, and extracted with Et_2O. The Et_2O layer was washed with brine; the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with 98:2 petroleum ether/ethyl acetate, yielding **8** as a white solid (52.0 mg, yield 70%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.09 (dt, 1H, J_1 = 8.06 Hz, J_2 = 0.92 Hz), 6.72–6.69 (m, 2H), 5.95–5.86 (m, 1H), 5.22–5.09 (m, 3H), 4.03–3.95 (m, 1H), 3.67–3.59 (m, 1H), 3.53–3.47 (m, 1H), 2.23–2.17 (m, 1H), 1.97–1.89 (m, 1H), 1.56 (s, 9H), 1.25 (t, 3H, J = 7.05 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 153.1, 152.1, 150.7, 141.3, 129.8, 121.8, 115.9, 113.9, 110.3, 98.8, 83.7, 64.6, 39.2, 34.2, 27.9, 15.4; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2980, 1757, 1614; MS FAB *m*/*z* 261 (24), 174 (54), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1616.

9: To a flame-dried 5-mL vial was added aldehyde **4** (30.1 mg, 0.089 mmol). Ethyl vinyl ether (**18**, 0.89 mL) was added and the vial was cooled to −78 °C. To this solution was added dimethylphenylsilyllithium (**30**, 740 μL, 0.27 mmol, 0.36 M in THF) dropwise. The reaction was stirred at −78 °C for 30 min. After $MgBr_2{\cdot}OEt_2$ (32.2 mg, 0.125 mmol) was added to the solution, the reaction was slowly warmed to room temperature. Upon completion, as noted by TLC, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine, and the combined aqueous layers were saturated with NaCl. After the saturated aqueous layer was washed with Et_2O, the combined Et_2O extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel eluting with 98:2 petroleum ether/ethyl acetate, yielding **9** as a white solid (32.8 mg, yield 86%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.54–7.52 (m, 2H), 7.38–7.36 (m, 3H), 6.75 (dd, 1H, J_1 = 8.42 Hz, J_2 = 0.73 Hz), 6.66 (d, 1H, J = 2.38 Hz), 6.57 (dd, 1H, J_1 = 8.42 Hz, J_2 = 2.56 Hz), 5.09–5.07 (m, 1H), 4.00–3.92 (m, 1H), 3.66–3.58 (m, 1H), 2.64–2.61 (m, 1H), 2.15–2.09 (m, 1H), 2.06–2.00 (m, 1H), 1.55 (s, 9H), 1.25 (t, 3H, J = 7.05 Hz), 0.32 (s, 3H), 0.26 (s, 3H); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 152.7, 152.1, 149.2, 139.5, 134.3, 129.1, 128.5, 128.0,

122.6, 113.6, 110.4, 98.3, 83.5, 64.4, 29.2, 27.9, 22.3, 15.3, −2.8, −3.9; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2983, 1757, 1613; MS (EI) *m*/*z* 148 (67), 135 (77), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{24}H_{32}O_5Si$ 428.2019, found 428.2018.

10: To a flame-dried 5-mL vial was added aldehyde **4** (32.0 mg, 0.095 mmol). Dihydropyran (**19**, 0.95 mL) was added and the vial was cooled to −78 °C. To this mixture was added MeMgCl (**31**, 37 μL, 0.104 mmol, 2.85 M in THF) dropwise. The reaction was slowly warmed to rt and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine; the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with 98:2 petroleum ether/ethyl acetate, yielding **10** as a white solid (20 mg, yield 66%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.11 (dt, 1H, J_1 = 7.69 Hz, J_2 = 1.28 Hz), 6.73–6.70 (m, 2H), 5.48 (d, 1H, J = 2.56 Hz), 4.00–3.94 (m, 1H), 3.77–3.73 (m, 1H), 3.14 (quintet, 1H, J = 6.41 Hz), 2.04–2.00 (m, 1H), 1.77–1.65 (m, 1H), 1.64–1.58 (m, 3H), 1.56 (s, 9H), 1.30 (d, 3H, J = 7.14 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 154.3, 152.2, 150.6, 127.2, 122.3, 113.8, 109.2, 97.5, 83.7, 61.1, 38.0, 32.0, 27.9, 24.7, 17.6, 15.4; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2978, 1758, 1613; MS (EI) *m*/*z* 220 (53), 205 (75), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1617.

11: To a flame-dried 5-mL vial was added aldehyde **4** (29.2 mg, 0.086 mmol). Enol ether **20** (116 mg, 0.86 mmol) and toluene (0.86 mL) were added and the vial was cooled to 0 °C. To this mixture was added MeMgCl (**31**, 46 μL, 0.14 mmol, 3 M in THF) dropwise. The reaction was slowly warmed to rt and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine, then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with 99:1 petroleum ether/ethyl acetate, yielding **11** as white solid (17.5 mg, yield 55%, inseparable mix of diastereomers). Major isomer: ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.61–7.28 (m, 5H), 7.17 (dd, 1H, J_1 = 8.42 Hz, J_2 = 0.92 Hz), 6.89 (d, 1H, J = 2.38 Hz), 6.79 (dd, 1H, J_1 = 8.42 Hz, J_2 = 2.38 Hz), 3.13 (s, 3H), 2.73 (sextet, 1H, J = 6.78 Hz), 2.15 (qd, 2H, J_1 = 42.3 Hz, J_2 = 13.73 Hz, J_3 = 6.23 Hz), 1.58 (s, 9H), 1.43 (d, 3H, J = 7.14 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 153.0, 152.2, 150.3, 141.2, 128.6, 127.5, 126.5, 125.6, 114.2, 110.2, 102.3, 101.0, 83.6, 50.3, 41.8, 27.9, 27.5, 22.2; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2967, 2935, 1758; MS (EI) *m*/*z* 255 (29), 223 (24), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{26}O_5$ 370.1780, found 370.1790.

General Procedure for Compounds 12 and 13

A flame-dried flask containing aldehyde **4** (0.1 M in Et_2O) was cooled to −78 °C. The appropriate organolithium reagent was added in dropwise fashion. After the mixture was stirred for 15 min, the dienophile (5 equiv) was added, followed 5 min later by $MgBr_2{\cdot}OEt_2$ (1 equiv), and the reaction was permitted to slowly warm to rt. Upon completion by TLC, 400 mg of silica gel was added to the solution suspended in 2 mL of Et_2O; the mixture was then stirred for 3 h. The reaction was then quenched with 1 M $NaHCO_3$ and extracted with an equal volume of Et_2O. The ether layer was washed with an equal volume of brine, and the organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo.

12: White solid (NMR yield 52%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.61 (s, 1H), 7.18 (d, 1H, J = 8.29 Hz), 6.94 (dd, 1H, J_1 = 8.29 Hz, J_2 = 2.3 Hz), 6.87 (d, 1H, J = 2.3 Hz), 3.93 (q, 1H, J = 6.76 Hz), 2.32 (s, 3H), 1.57 (s, 9H), 1.27 (d, 3H, J = 6.91 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 195.9, 152.0, 150.1, 129.7, 124.3, 122.0, 118.2, 109.9, 84.1, 77.4, 29.9, 27.9, 27.3, 25.6, 25.5; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2928, 1759, 1644, 1587, 1501; MS (EI) *m*/*z* 204 (21), 189 (90), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1315.

13: Brown oil (NMR yield 56%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.95 (d, 2H, J = 7.37 Hz), 7.58 (t, 1H, J = 7.37 Hz), 7.45 (t, 2H, J = 7.7 Hz), 7.18 (d, 1H, J = 8.29 Hz), 6.76–6.72 (m, 2H), 3.78–3.73 (m, 1H), 3.47 (dd, 1H, J_1 = 18.77 Hz, J_2 = 9.52 Hz), 3.29 (dd, 1H, J_1 = 18.58 Hz, J_2 = 3.22 Hz), 1.54 (s, 9H), 1.41 (d, 3H, J = 7.06 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 201.8, 154.8, 152.2, 150.3, 136.2, 134.0, 130.8, 128.9, 128.6, 127.1, 114.1, 111.2, 83.6, 48.7, 27.9, 26.2, 21.7; IR [CH_2Cl_2, ν_{max} cm^{-1}] 3686, 3053, 2960, 2928, 2855, 1755, 1733, 1671, 1599; MS (EI) *m*/*z* 281 (60), 57 (74), 43 (100); HRMS (EI) *m*/*z* $(M + Na)^+$ calcd for $C_{21}H_{24}O_5Na$+ 379.1521, found 379.1527.

14: To a flame-dried 5-mL vial was added aldehyde **4** (32.5 mg, 0.096 mmol). Diethyl ether (0.96 mL) and enamine **23** (161 μL, 0.96 mmol) were added and the vial was cooled to −78 °C. To this mixture was added vinylmagnesium chloride (**29**, 110 μL, 0.106 mmol, 0.955 M in THF) dropwise. The reaction was slowly warmed to rt and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine; the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with 98:2 petroleum ether/ethyl acetate, yielding **14** as a white solid (28.0 mg, yield 70%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.06 (dt, 1H, J_1 = 8.06 Hz, J_2) 0.916 Hz), 6.67–6.64 (m, 2H), 5.87–5.78 (m, 1H), 5.22–5.14 (m, 2H), 3.70–3.60 (m, 4H), 3.36–3.32 (m, 1H), 2.82–2.71 (m, 4H), 2.15–2.10 (m, 1H), 1.84–1.72 (m, 3H), 1.66–1.56 (m, 12H), 1.49 (s, 1H), 1.42–1.36 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 153.4, 152.2, 150.9, 142.1, 130.3, 120.8, 116.3, 113.1, 109.8, 91.6, 83.4, 67.6, 45.0, 44.0, 38.0, 29.9, 28.0, 27.8, 22.6, 22.1; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2936, 2858, 1757, 1610, 1591, 1498; MS (EI) *m*/*z* 167 (100), 57 (14), 43 (15); HRMS (EI) *m*/*z* calcd for $C_{24}H_{33}NO_5$ 415.2359, found 415.2348.

15: To a flame-dried 5-mL vial was added aldehyde **4** (33.3 mg, 0.098 mmol). Ether (1 mL) and imine **24** (100 μL, 0.49 mmol) were added and the vial was cooled to −78 °C. To this mixture was added MeMgCl (**31**, 41 μL, 0.108 mmol, 2.65 M in THF) dropwise. The reaction was slowly warmed to rt and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine; the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with petroleum ether, yielding **15** as a white solid (40.0 mg, yield 94%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.77–7.75 (m, 2H), 7.45–7.41 (m, 2H), 7.35–7.29 (m, 5H), 7.25–7.22 (m, 1H), 6.99 (d, 1H, J = 8.42 Hz), 6.89 (d, 1H, J = 2.38 Hz), 6.75 (dd, 1H, J_1 = 8.42 Hz, J_2 = 2.38 Hz), 6.09 (s, 1H), 3.86–3.79 (m, 2H), 3.34 (d, 1H, J = 14.83 Hz), 1.59 (s, 9H), 1.55 (d, 1H, J = 6.96 Hz); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 154.8, 152.3, 150.3, 139.6, 138.2, 129.3, 128.5, 128.4, 128.2, 128.1, 127.0, 126.7, 123.0, 114.1, 110.2, 86.0, 83.8, 52.4, 49.8, 27.9, 24.1; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2975, 2935, 1758, 1617; MS FAB *m*/*z* 136 (27), 91 (100) 57 (82); HRMS (EI) *m*/*z* calcd for $C_{27}H_{29}$-NO_4 431.2097, found 430.2113.

16: To a flame-dried 5-mL vial was added aldehyde **4** (36.2 mg, 0.107 mmol). Furan (**25**, 1.07 mL) was added and the vial was cooled to −78 °C. To this mixture was added MeMgCl (**31**, 48 μL, 0.118 mmol, 2.45 M in THF) dropwise. The reaction was slowly warmed to rt and monitored by TLC. Upon completion, the reaction was quenched with 1 M $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was washed with brine; the combined aqueous layers were saturated with NaCl and extracted with Et_2O. The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed through silica gel, eluting with 98:2 petroleum ether/ethyl acetate, yielding **16** as a white solid (24.7 mg, yield 76%). ^{1}H NMR [$CDCl_3$, 400 MHz] δ 7.15 (dd, 1H, J_1 = 8.24 Hz, J_2 = 1.28 Hz), 6.83 (dd, 1H, J_1 = 8.24 Hz J_2 = 2.38 Hz), 6.71 (d, 1H, J = 2.38 Hz), 6.39–6.37 (m, 1H), 5.5 (ddd,

1H, J_1 = 8.24 Hz, J_2 = 2.56 Hz, J_3 = 0.92 Hz), 5.07 (td, 1H, J_1 = 2.56 Hz, J_2 = 0.37 Hz), 4.92 (dd, 1H, J_1 = 8.24 Hz, J_2 = 2.93 Hz), 3.08 (qd, 1H, J_1 = 6.96 Hz, J_2 = 2.93 Hz), 1.58–1.53 (m, 12H); ^{13}C NMR [$CDCl_3$, 100 MHz] δ 155.2, 152.0, 151.8, 150.4, 126.6, 126.2, 115.1, 111.9, 101.5, 85.2, 83.6, 82.3, 31.1, 27.9, 13.7; IR [CH_2Cl_2, ν_{max} cm^{-1}] 2975, 2935, 1758, 1612; MS (EI) *m*/*z* 189 (46), 136 (27), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1316.

Acknowledgements

Research support from the University of California Coordinating Committee on Cancer Research in the form of two awards (19990641 and SB010064) is greatly appreciated along with additional support from NSF (CHE-9971211), PRF (PRF34986-G1), NIH (GM-64831), the UC-AIDS Initiative (K00-SB-039), and Research Corporation (R10296). We are also thankful for the support of our M.S. facility funded in part by DAAD19-00-1-0026.

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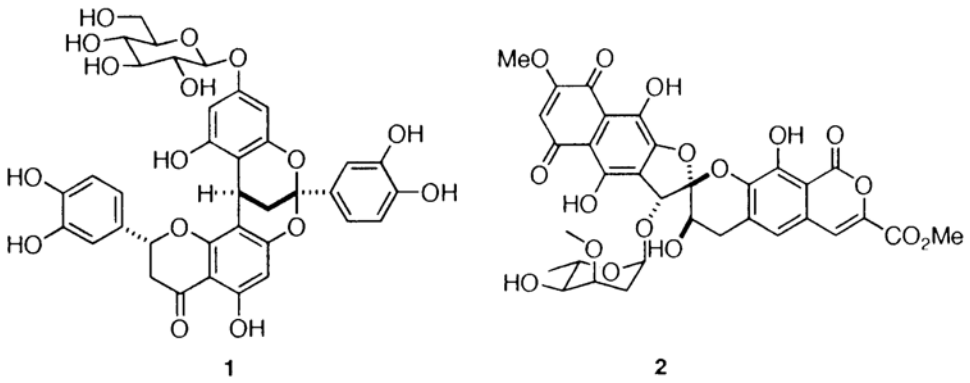


FIGURE 1.
Examples of biologically active benzopyrans.

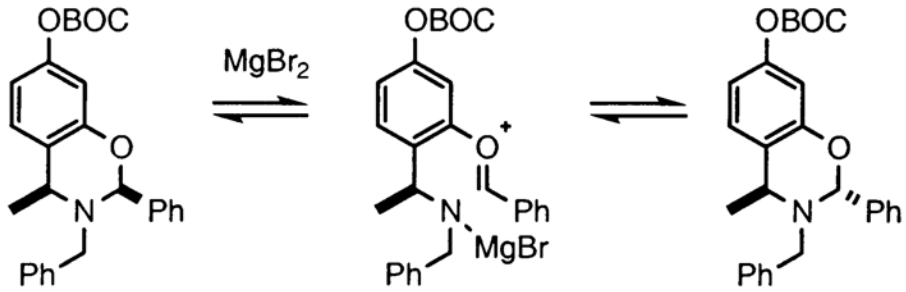
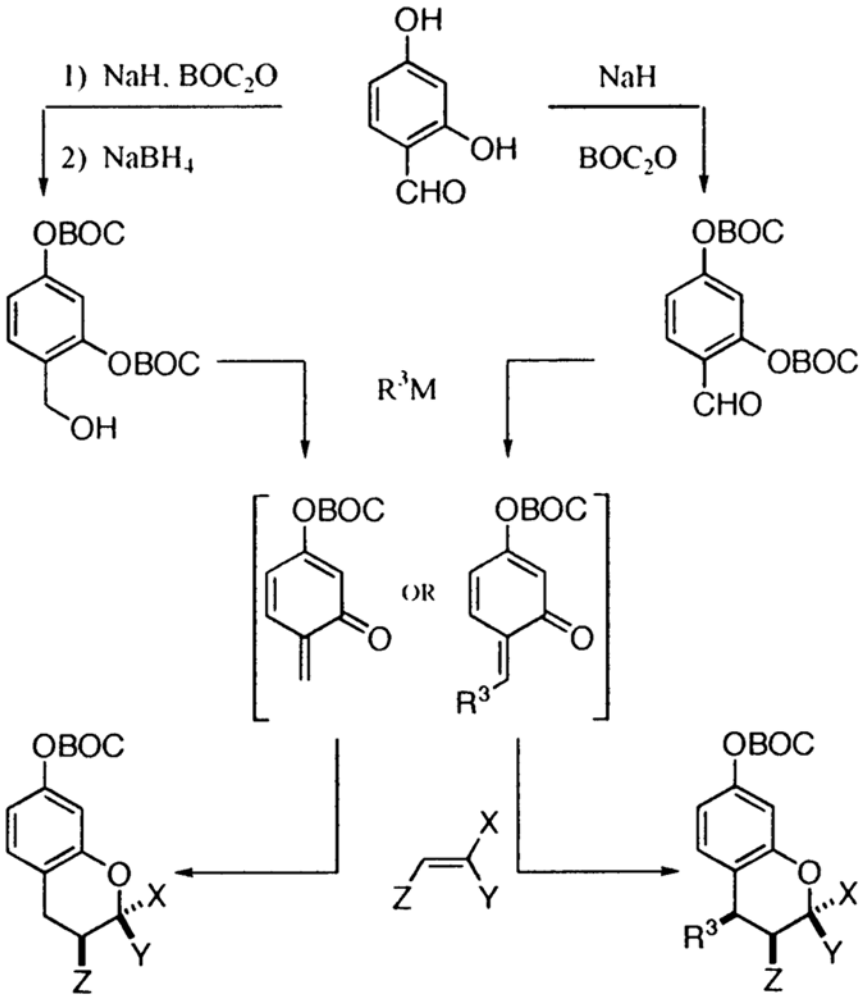


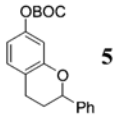
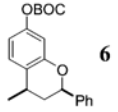
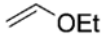
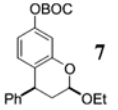
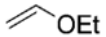
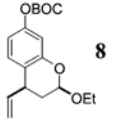
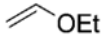
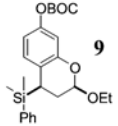
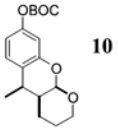
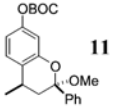
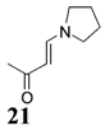
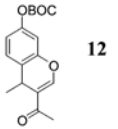
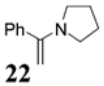
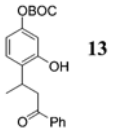
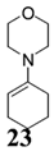
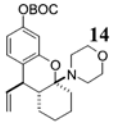
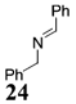
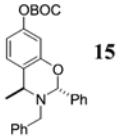
FIGURE 2.
Equilibration of the stereochemistry in **15**.



Scheme 1.
Cycloadditions of Salicylic Aldehydes and Alcohols

TABLE 1

One-Pot Diastereoselective Benzopyran Synthesis

	SM	R′M	2π	Cycloadduct	*cis/trans*[a]	%
1[b]	**3**	*t*-BuMgCl **26**	 **17**	 **5**	NA	50
2[b]	**4**	MeLi **27** + $MgBr_2$	 **17**	 **6**	~6:1	27
3[b]	**4**	PhMgBr **28**	 **18**	 **7**	>50:1[c]	73
4[b]	**4**	 **29**	 **18**	 **8**	>50:1[c]	70
5[b]	**4**	 **30** + $MgBr_2$	 **18**	 **9**	>50:1[c]	86
6[b]	**4**	MeMgCl **31**	 **19**	 **10**	~24:1	66
7[d]	**4**	MeMgCl **31**	 **20**	 **11**	~4:1	55
8[e]	**4**	MeLi **27** + $MgBr_2$	 **21**	 **12**	NA	57
9[e]	**4**	MeLi **27** + $MgBr_2$	 **22**	 **13**	NA	58
10[d]	**4**	 **29**	 **23**	 **14**	>50:1[c]	70
11[e]	**4**	MeMgCl **31**	 **24**	 **15**	<1:50[c]	94
12[b]	**4**	MeMgCl **31**			>50:1[c]	76

[a] Cis/trans ratio determined by ^{1}H NMR analysis of crude material.

[b] 2π component used as the solvent for the reaction.

[c] >50:1 signifies that no other isomers could be found in the 400-MHz ^{1}H NMR spectra.

[d] 5–10 equiv of 2π component used.

[e] 2–5 equiv of 2π component used.